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Surgical Staging and Adjuvant Immunotherapy for Early Melanoma - Case Study

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Abstract: ***Malignant melanoma (MM) is a malignant disease arising from melanocytes and primarily affecting the skin. Most newly diagnosed cases lack metastatic data, with 71.5% in stages I-II. The majority are in stage II (42.7%), indicating a prevalence of locally advanced tumors (stage T2b and above) without evident metastasis at the time of diagnosis. These patients remain under active surveillance while being at increased risk of disease progression. The role of surgery is shifting from an exclusive method for radical treatment towards increasingly serving as an early staging method to refine adjuvant therapy for these patients. With the abandonment of elective (prophylactic) lymph node dissections in early melanoma without clinical evidence of regional metastasis, SLNB (Sentinel Lymph Node Biopsy) becomes the sole method for detecting micrometastases in these patients. With a higher percentage of detected subclinical metastases and fewer intra- and post-operative complications, amidst increasing needs for early staging with new adjuvant treatment regimens in the early stages of the disease, SLNB has solidified its position as a widely used procedure with expanded indications. In the era of modern adjuvant treatment for early melanoma, SLNB surgery plays a crucial role in accurate staging and risk determination in patients, aiming to refine subsequent treatment and follow-up.***

Keywords: early melanoma, sentinel node, staging, adjuvant therapy

1. Introduction

Malignant melanoma (MM) is a malignant disease arising from melanocytes and primarily affecting the skin. Despite constituting only 4% of all skin neoplasms, it accounts for up to 80% of all deaths from these diseases, making early diagnosis crucial. Globally, according to Globocan data, there is a stable annual increase in incidence by 3-5%, with over 600 new cases registered annually in Bulgaria [1]. Malignant melanoma is classified as a rare malignant disease in Bulgaria [2] with an incidence of 37/100,000 according to the latest National Cancer Register data from 2016 [3]. Mortality is 21/100,000, meaning more than half of the patients die as a result of the disease. Despite efforts for early diagnosis in the country, at the time of initial diagnosis, 24.3% of patients already have lymphatic or hematogenous metastases, and 16% develop hematogenous ones without lymph node involvement. MM spreads via the lymphatic pathway to the regional lymphatic basin, metastasizing to the regional lymph nodes (RLNs) in 80% of cases within the first 2 years. Most newly diagnosed cases lack metastatic data with 71.5% in stages I-II. The majority are in stage II (42.7%), indicating the prevalence of locally advanced tumors (stage T2b and above) without evident metastasis at the time of diagnosis. These patients remain under active surveillance while being at increased risk of disease progression.

Sentinel Lymph Node Biopsy in Light of Modern Drug Therapy

Historically, sentinel lymph node biopsy (SLNB) for malignant melanoma was introduced by Morton [4] as a method for selecting patients eligible for radical lymph node dissection. It serves as a staging method for early detection of micrometastases in regional lymph nodes. Patients in whom such are detected undergo radical dissection, while those without micrometastases in sentinel nodes remain under active surveillance, sparing them unnecessary surgical interventions and potential complications. Successes in modern systemic therapy for stage III patients have led to a reevaluation of this paradigm.

The last 10 years have marked a fundamental change in the therapeutic strategy for malignant melanoma. The question arose whether radical dissection is justified in patients with micrometastases in sentinel nodes. Two randomized clinical trials have been published so far, comparing the outcomes of immediate complete dissection versus observation in patients with positive sentinel nodes: DeCOG (German Dermatologic Cooperative Oncology Group Selective Lymphadenectomy) [5] and MSLT-2 (Multicenter Selective Lymphadenectomy Trial) [6]. Based on the results of these studies, we can summarize that complete dissection after a positive sentinel node does not improve survival. The frequency of metastases in non-sentinel nodes with a positive sentinel node is 15-20%, but complete dissection leads to upstaging and improved staging in less than 6% of cases. Complete dissection improves local control in the subgroup of patients with lymphatic metastases without affecting survival. At the same time, MSLT-II clearly shows a much higher rate of complications with radical dissection. ESMO does not recommend performing radical dissection with a positive sentinel node. If patients do not meet the criteria for adjuvant treatment, they should be monitored with ultrasound, and in the case of metastases in RLNs, a complete dissection should be performed. NCCN recommends discussing the benefits and risks of complete lymph node dissection with the patient after a positive sentinel node, with the preferred approach being observation.

In 2010, modern systemic treatment for malignant melanoma with immunotherapy was introduced with the first antibody from the anti-CTLA-4 class, ipilimumab. A revolutionary advance in the treatment not only of MM but also of various oncological diseases followed. The next year

(2011) saw the introduction of the first targeted agent, the BRAF inhibitor vemurafenib. Currently, oncology has a large arsenal of mono and combined immuno- and targeted therapies. A significant achievement is that as of 2023, the 5-year survival rate for stage IV MM exceeds 50%, compared to only 5% in the past, allowing us to view skin MM as a chronic oncological disease with a controllable course [7]. While in the past surgical treatment was considered the only guaranteed cure for early melanoma, today it is largely equated with drug therapy [8].

With the abandonment of elective (prophylactic) lymph node dissections in early melanoma without clinical evidence of regional metastasis, SLNB is the sole method for detecting micrometastases in these patients. The higher percentage of detected subclinical metastases with fewer intra- and postoperative complications amid growing needs for early restaging with new adjuvant treatment regimens in the early stages of the disease has established sentinel biopsy as a widely used procedure with expanded indications [9]. It should be noted that the latest 8th edition of the TNM classification requires SLNB for patient staging. Sentinel biopsy is primarily a procedure for early restaging from stage I and II to stage III. Improvement in survival is observed only in patients with intermediate risk – tumor thickness 1.2 – 3.5 mm. The presence of micrometastases in the sentinel node is the most important prognostic factor in primary melanoma, confirming the already initiated metastatic process, with the highest statistical significance – $P < 0.00001$ [10, 11].

There is agreement in modern guidelines [12, 13] regarding the indications for SLNB:

- Breslow tumor thickness over 0.8 mm with or without signs of ulceration;
- Less than 0.8 mm with signs of ulceration;
- There must be no clinical and imaging suspicions or evidence of already metastatic lymph node involvement.

Since 2019, after reassessing the risk of distant dissemination in operable stage III, adjuvant treatment regimens have been registered for one year following complete resection, regardless of the size of the tumor metastasis in the lymph node or its type in the respective stage. Indications for adjuvant treatment are [14]:

1) All patients with micrometastases localized via SLNB
2) Macrometastases after radical lymph node dissection
3) Those after isolated radical metastasectomies in stage III of satellites and in-transit metastases.

In Bulgaria adjuvant combined targeted therapy is registered for BRAF-positive patients with the drugs Dabrafenib+Trametinib and adjuvant monoimmunotherapy regardless of BRAF status with anti-PD1 antibody Pembrolizumab and Nivolumab. Five-year survival data are almost identical for the combination of BRAF + MEK inhibitors and immunotherapy with anti-PD1 antibodies, exceeding 50%.

The accumulated experience over 10 years with various adjuvant regimens has revolutionized the treatment of melanoma (MM), and today we have a variety of therapeutic tactics and strategies. Thanks to modern targeted and immunotherapy, more than half of patients in advanced stages are alive at the 5-year mark compared to less than 10% in 2011. Our aim today is not just to prolong the life of patients but to turn MM into a chronic disease that is well-controlled. The role of surgery is shifting from an exclusive method for radical treatment to increasingly serving as an early staging method to refine adjuvant therapy [15].

Among melanoma (MM) patients with the best and similar melanoma-specific survival rates at 5 and 10 years, reaching up to 99%, are those in the earliest stages IA and IB [16, 17]. However, when examining data for other stages, we find that patients in stages IIB and IIC, or with a tumor thickness over 2 mm according to Breslow, have melanoma-specific survival rates at 5 years close to those of stage IIIB. These are high-risk patients who, despite having no clinical evidence of metastases in regional lymph nodes, likely already have undiagnosed micrometastases. Nearly 17% of patients in stages IIC and IIIB subsequently develop distant metastases. Surgical staging through SLNB (Sentinel Lymph Node Biopsy) and the detection of micrometastases in the sentinel node allow for appropriate determination of subsequent therapy in these patients [18]. The significant risk has led to justified concerns that early stage IIB, and particularly IIC, prognostically approach stage IIIB and also require adjuvant treatment. This led to the study and approval in June 2022 of the drug Pembrolizumab in an adjuvant regimen specifically for these stages, with a treatment duration of 1 year.

The presence of regional metastases outside the lymph nodes (microsatellites, satellites, and in-transit metastases) is a poor prognostic indicator (19) and is denoted by the index "c" in the N category. Microsatellites refer to all microscopic nests of tumor cells in the skin or subcutaneous tissue near, but separate from, the primary tumor. Satellites are clinically detectable metastases in the skin or subcutaneous tissue located up to 2 cm from the primary melanoma but not connected to it. In-transit metastases are all clinically detectable metastases in the skin and subcutaneous tissue located more than 2 cm from the primary tumor but not beyond the regional lymph basin. They represent metastases in the lymphatic vessels leading to the regional lymph nodes. The presence of microsatellites, clinically detected satellites, or in-transit metastases signifies the development of the metastatic process from the primary tumor to the regional lymph nodes and is typically classified as stage IIIC.

The significance of SLNB (Sentinel Lymph Node Biopsy) is not well studied in the presence of satellitosis, as it does not result in a stage increase from I-II to III. Patients with microsatellites in the excisional biopsy specimen or visible satellites and in-transit metastases are automatically classified at least as stage pN1c, which corresponds to at least stage IIIB. SLNB has prognostic significance for these patients as well since a positive sentinel node would elevate the stage to pN2c, corresponding to at least stage IIIC. Given the dynamic development of recommendations for systemic treatment, detailed staging in stage IIIB or IIIC can be important. If SLNB would lead to a change in therapeutic approach, it should be considered and performed even in such patients. There are also special cases of the presence of

in-transit metastases with negative sentinel nodes. SLNB is particularly effective in restaging these patients.

Clinical Case

We present a clinical case of a 49-year-old patient who was operated on at another medical facility for a superficially spreading malignant melanoma in the left lumbar region, with an excisional biopsy performed at stage pT4b. Ultrasound staging did not reveal any enlarged lymph nodes, which places the patient at clinical stage IIC. According to international guidelines, the patient is eligible for sentinel lymph node biopsy (SLNB), which was conducted at the University Hospital for Active in Oncology, Sofia, Bulgaria, one month after the excision. Lymphoscintigraphy and SPECT/CT performed at the Department of Nuclear Medicine identified two sentinel lymph nodes in the left axilla, and an additional finding of a hyperfixative focus in the left lumbar area with the appearance of a nodular structure (Fig. 1).

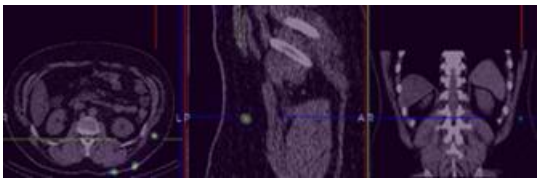

Figure 1: Hyperfixative focus in the left lumbar region with the appearance of a nodular structure identified on SPECT/CT. Additional activity is also seen at the injection sites around the scar.

The described focus is not palpable due to its deep subcutaneous location and is highly suspicious for an in-transit metastasis. It has been marked on the patient's skin by the nuclear medicine physician who conducted the examination (Fig. 2).

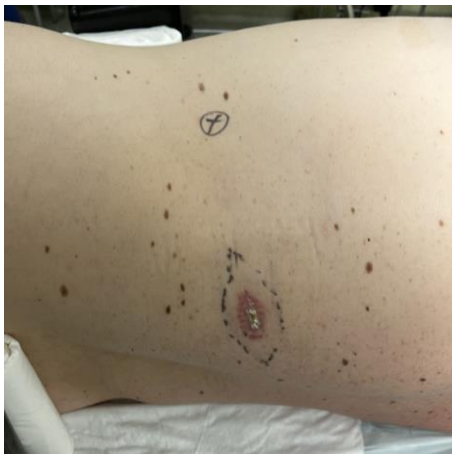

Figure 2: The patient is positioned on the operating table in the right lateral position. The planned re-excision of the scar in the area of the primary tumor has been marked, and the projection of the in-transit node on the skin has been noted.

After re-excision of the scar 1.5 cm to radical margins using a surgical gamma probe and an incision in the left lumbar area, the hyperfixative focus was identified. An in-transit node with brown pigmentation in a single area was found (Fig. 3).

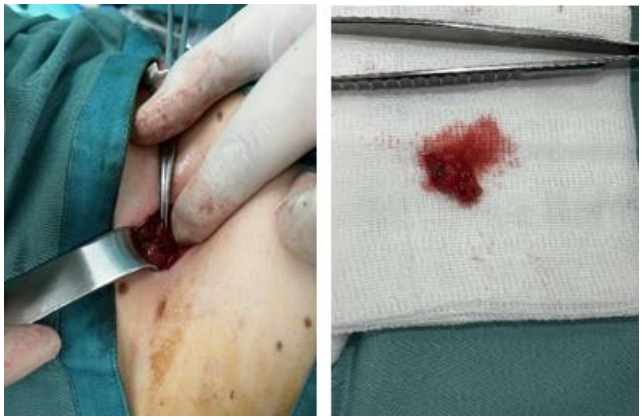

Figure 3: In-transit lymph node in the left lumbar region – intraoperative finding and macroscopic appearance.

The described two sentinel lymph nodes in the left axilla were also identified using a surgical gamma probe and removed. Histological examination did not reveal metastases in the sentinel lymph nodes. The in-transit node was found to be a lymph node measuring 13 mm with discontinuous subcapsular tumor metastases from malignant melanoma, the largest of which was 4 mm. The stage was determined as pT4bpNsn1a(0)cM0, BRAF (+). Subsequently, a staging PET/CT was performed to search for additional metastatic lesions, but none were found. The presence of an in-transit metastasis, despite the negative regional lymph nodes, staged the patient at IIIC, and adjuvant systemic treatment was initiated.

2. Discussion and Recommendations

Upon diagnosis, patients without evidence of metastases should be considered as either low-risk or high-risk. High-risk patients are likely to have occult metastatic disease and subsequent progression. In the era of modern adjuvant therapy, these patients need to be identified in a timely manner, with the surgeon playing a key role. In the absence of effective prognostic markers for biological tumor aggressiveness, Sentinel Lymph Node Biopsy (SLNB) is the most effective method for assessing prognosis. It helps us identify occult oligometastatic stages (known as "hidden stage III"), including cases where only in-transit metastases are present without involvement of regional lymph nodes, which are at higher risk of progression. Determining the risk would assist and motivate the decision for initiating adjuvant immunotherapy in stages IIB and IIC, regardless of age, to achieve better disease control. While for stage II patients, we only have adjuvant immunotherapy, in stage III for BRAF-positive patients, we have a range of options between immunotherapy and targeted therapies. This choice should consider numerous factors and be individualized according to the specific needs of the patient. This is why we use the concepts of micro- and macrometastatic disease in regional lymph nodes to clearly define tumor volume and the risk of distant metastases. Satellite and in-transit metastases should not be overlooked as part of stage III, but it is appropriate, when there is isolated dissemination without involvement of regional lymph nodes or the "N1c" category, to consider them in the treatment decision as an oligometastatic variant of macrometastatic disease in regional lymph nodes, due to the significant difference in tumor burden. When in-transit lymphogenic metastases are detected via SLNB with

micrometastases under 2 mm, it is referred to as an in-transit micrometastatic process and is categorized on the same principle as "N1c." There is also a difference in the follow-up regimen, which should be much more intensive and involve more imaging studies for patients at high risk of progression.

In the era of modern adjuvant therapy for early melanoma, surgery using Sentinel Lymph Node Biopsy (SLNB) plays a crucial role in accurate staging and risk assessment of patients, aiming to refine subsequent treatment and follow-up. To provide the best chance for survival for these patients, they should be directed to centers with experience and capabilities in performing SLNB.

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Author Profile

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